Application of Sonogashira and Baylis–Hillman reactions with β-trifluoromethylated acroleins

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The reaction of alkynes with 2-phenyl-3-iodo-4,4,4-trifluorobut-2-enal in the presence of palladium (0) is reported (Sonogashira reaction). Moreover, 2-(hydroxytrifluoromethylalkenyl)cyclohexenones have been prepared by the reaction of cyclohexenone and β-trifluromethylacroleins in the presence of *N*-methylimidazole catalysis.

Keywords: β- trifluoromethylenynes, palladium (0), cyclohexenone, *N*-methylimidazol catalysis, Baylis–Hillman adducts

Organofluorine compounds have found increasing use in the areas of agrochemicals, pharmaceuticals, polymers and new materials.[1–5] The fluorine atom brings specific chemical and physical properties to molecules in the pharmaceutical field. Molecules containing CF_2 or CF_3 can offer a significant change in biological activity, compared to their non fluorinated analogues. For example, the enzyme inhibitory activity of trifluoromethylketones has been widely proved.[6] The interest in molecules containing the CF_3 group entailed the development of new and efficient synthetic methodologies.

In particular, the formation of C–C bond and the transformation of functional groups are fundamental processes for organic synthesis. Recently, the catalysis by the transition metals and Baylis–Hillman reaction have been the focus of research.[7–13]

In connection with our interest in the synthesis and the reactivity of trifluoromethylated Vilsmeir adducts,[14,15] we considered the Sonogashira reaction with the acrolein **1**[16] and the Baylis–Hillman reaction towards trifluoromethylated acroleins **5a–f**.[17,18]

Palladium-catalysed coupling reaction; synthesis of trifluoromethylatedenynes (**3a–c)**: This reaction is useful for the preparation of biological polymers.[19] It consists of introducing an sp^2 hybrid organic substratum to acetylenic one: (sp^2-sp coupling). The utilisation of a co-catalysis (CuI) expedites the acetylenic substratum easing the reaction with the palladium complex (0). By utilising Sonogashira coupling, the reaction of the acrolein **1** with alkynes **2a–c** has given trifluoromethylated enynes **3a–c**; each one formed as a mixture of *Z* and *E* diastereomeres. We have observed that the *E:Z* ratios of these compounds depend on the nature of the alkynes and can be determined by ^{19}F NMR spectroscopy. An anisotropic effect for the phenyl moiety on to the CF_3 group was observed in the case of the (Z)-**3** diastereomers (Scheme 1).

N-Methylimidazole-catalysed Baylis–Hilman reactions: synthesis of 2-(hydroxytrifluoromethylalkenyl)cyclohexenon es from β-trifluromethylated acroleins and cyclochexenone

The Baylis–Hillman reaction is a useful and general σ C–C bond-forming reaction providing a straight forward single-step synthetic method to form densely functionalised precursors.[20,21] Their versatility has made these multifunctionalised compounds valuable synthetic intermediates[22,23] and has also stimulated their utilisation as substrates for chemical transformation mediated by palladium, especially for Heck reactions.[24,25]

In continuation of our study on α-functionalisation of cyclic enones, we now report our results on the N-methylimidazole mediated Baylis–Hillman reaction between cyclic enones and trifluoromethylated acroleins **5a–f)**. We have found the 2-(hyd roxytrifluoromethylalkenyl)cycloxenones **6a–f)** (Scheme 2).

In conclusion, we describe in this work the synthesis of trifluoromethylated enynes **3a–c)** by palladium catalysis coupling reaction. The products obtained can be precursors for the synthesis of biological heterocyclic such as Neocarzinstatine which has antitumor activity.[26]

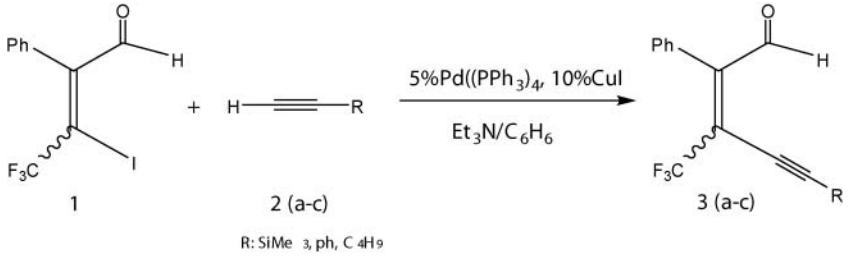
The Baylis–Hillman adducts **6–f** can be used as intermediates in the synthesis of natural products.[27] However, we have varied the operation conditions to ameliorate yields and to reduce the reaction time.

Experimental

All reactions progress was monitored by TLC analysis (Merck Kieselgel 60 F_{254}). All compounds were purified by chromatography column (Silica gel 60. 70–230 mesh ASTM). IR spectra were obtained on Perkin-Elmer Paragon 1000 PC. ^1H NMR spectra were recorded on a Bruker AC-300 (300 MHz) spectrometer using tetramethylsilane (TMS, δH, 0) as internal standard. ^{13}C NMR spectra were recorded on Bruker AC-300 (75 MHz) spectrometer with proton decoupling. For ^{19}F NMR spectra, C_6F_6 was used as reference and they were performed on a Bruker AC-300 (282.36 MHz). Mass spectra were carried out on a Hewlett-Packard model (70 eV) by the staff of the Faculty of Medicine, Department of Biochemistry, Monastir, Tunisia, under electronic impact (EI). Elemental analyses were performed by the microanalyses service of the Centre of Pharmaceutical Studies, Châtenay-Malabry. Coupling constants (*J* values) are given in Hertz and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet).

*Typical procedure for the synthesis of compound **3a–c***

To a solution of the acrolein **1** (3×10^{-4} mol) in the benzene, we are added under argon atmosphere and at room temperature, the $Pd^0(PPh_3)_4$



Scheme 1

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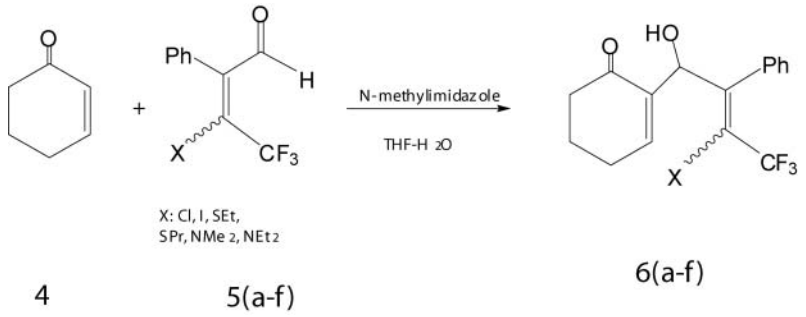

Scheme 2

(5%), CuI (10%), Et_3N (6×10^{-4} mol) and the alkynes **2a–c**). The mixture was stirred at room temperature the evolution of the reaction was followed by gaseous phase chromatography and quenched with NH_4Cl. The organic layer was separated and the aqueous phase was extracted with ether (3×15 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. The product was purified by column chromatography, filled with silica gel and elution with ethyl ether-petroleum ether (20/80).

2-phenyl-3-trifluoromethyl-5-trimethylsilanylpent-2-en-4-ynal (**3a**): Colourless oil. Yield: 80%. IR ν (cm^{-1}): 1692 (CO); 1155–1148 (CF_3); ^{1}H NMR (400 MHz, $CDCl_3$): 0.2 (2s, 9H); 7.3 (m, 5H); 10 (q, 1H); 10.3 (s, 1H); ^{13}C NMR (75,47 MHz, $CDCl_3$): 14.2–14.6 (2s, CH_3); 122.1–122.6 (2q, CF_3); 128–130.3 (m, C_6H_5); 192–191.7 (2s, CHO); ^{19}F NMR (282.4 MHz; $CDCl_3$): *E*:*Z*: 5/95. δ_F: 109 (s, CF_3); 111 (s, CF_3). Anal Calcd for $C_{15}H_{15}F_3OSi$: C, 60.78; H, 5.10 . Found: C, 60.72; H, 5.28%.

2,5-diphenyl-3-trifluoromethylpent-2-en-4-ynal (**3b**): Yellow oil. Yield: 85 %. IR. ν (cm^{-1}): 1690 (CO); 1148–1185 (CF_3); ^{1}H NMR (400 MHz, $CDCl_3$): 7.5 (m, 10H); 10.3 (q, 1H); 10.6 (s,1H); ^{13}C NMR (75,47 MHz, $CDCL_3$): 122.8–122.3 (2q, CF_3); 128.15–131.5 (m, $2C_6H_5$); 137 (CCF_3); 147.31 (C–C–CF_3); 192.6–191.83 (2s, CHO); ^{19}F NMR(282.4 MHz; $CDCl_3$): *E*:*Z*= 13/87. δ_F: 103.5 (s, CF_3); 109 (s, CF_3). Anal Calcd for $C_{18}H_{11}F_3O$: C, 71.98; H, 3.69. Found C, 71.7; H, 3.28%.

2-phenyl-3-trifluoromethylnon-2-en-4-ynal (**3c**): Colourless oil. Yield: 78%. IR. ν (cm^{-1}): 1698 (CO); 1158.17–1134 (CF_3); ^{1}H NMR (400 MHz, $CDCl_3$):0.7 (t, 3H); 1.4 (m, 4H); 2.1 (m, 2H); 7.3 (m, 5H); 10.4 (s, 1H); ^{13}C NMR (75,47 MHz, $CDCL_3$): 13.58–14.8 (m, $(CH_2)_2CH_3$); 47.53–48.7 (2s, CH_2); (121.7; 122) (2q, CF_3, $^1J_{CF}$ = 282.7 Hz); 127.3–130.2 (m, C_6H_5); 134 (q, CCF_3, $^2J_{CF}$ = 30.18 Hz); 145.22 (C–C–CF_3); (191.7; 190.6) (2s, CHO); ^{19}F NMR (282.4 MHz; $CDCl_3$): *E*:*Z* = 10/90. δ_F: 108.8 (s,CF_3); 110.5 (s,CF_3). Anal Calcd for $C_{16}H_{15}F_3O$: C, 68.54; H, 5.39. Found C, 68.78; H, 5.43%.

Preparation of 2-(3-chloro-4,4,4-trifluoro-1-hydroxy-2-phenylbut-2-enyl)-cyclohex-2-en-1-one (**6a**): A 50 mL round-bottomed flask was charged with cyclohexenone (0.48, 5mmol), 10 mmol of the acrolein **5a** 3mL of THF and 3mL of H_2O and N-methylimidazole (0.05g, 0.5mmol). The resulting mixture was stirred for 40 days at 60 °C. When the reaction, followed by TLC was finished, the mixture was acidified with aqueous HCl (1.5M) and extracted with methylene-chloride. After the usual work up, chromatography of crude product on silica gel, using ether as eluent, gave pure 2-(3-chloro-4,4,4-trifluoro-1-hydroxy-2-phenylbut-2-enyl)-cyclohex-2-en-1-one **6a**.

2-(3-chloro-4,4,4-trifluoro-1-hydroxy-2-phenylbut-2-enyl)-cyclohex-2-en-1-one (**6a**): Yellow oil. Yield: 45%. 40 days. IR ν (cm^{-1}): 3397 OH); 1686 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): 1.2 (m, 6H); 4.1 (s, 1H); 4.9 (OH); 7.4 (m, 5H); 7.6 (m, 1H); ^{13}C NMR (75,47 MHz, $CDCL_3$): 22.89; 26.31; 39.15; 61.23; 120.04; 127.4; 128.9; 127.53–130.5; 138 .78; 147.84; 205. ^{19}F NMR (282.4 MHz; $CDCl_3$): δ_F: 80.84; MS (*m/z*): 206 (30); 222 (45); 69 (78); 330 (25); 279 (36). Anal Calcd for $C_{16}H_{14}F_3ClO_2$: C, 58.07; H, 4.27. Found C, 58.23; H, 4.06%.

2-(4,4,4-trifluoro-1-hydroxy-3-iodo-2-phenylbut-2-enyl)-cyclohex-2-en-1-one (**6b**): Yellow oil. Yield: 44%. 45 days. IR ν (cm^{-1}): 3383 (OH); 1672 (CO); ^{1}H NMR (400 MHz, $CDCl_3$): 1.3 (m, 6H); 3.9 (s, 1H); 4.3 (OH); 7.2 (m, 5H); 7.3 (m, 1H); ^{13}C NMR (75,47 MHz, $CDCL_3$): 22.36; 25.69; 38.41; 61.07; 118.34; 125.98; 127.3; 127.21–130.1; 135 .87; 146.71; 203. ^{19}F NMR (282.4 MHz; $CDCl_3$): δ_F: 81.31 Anal Calcd for $C_{16}H_{14}F_3IO_2$: C, 45.49; H, 3.34. Found C, 45.53; H, 3.26%.

2-(3-ethylsulfanyl-4,4,4-trifluoro-1-hydroxy-2-phenylbut-2-enyl) cyclohex-2-en-1-one (**6c**): Colourless oil. Yield: 55%. 22 days. IR ν (cm^{-1}): 3406 (OH); 1669 (CO); 1167 (CF_3); ^{1}H NMR (400 MHz, $CDCl_3$): 0.85 (t, 3H); 2 (q, 2H); 2.38 (m, 6H); 6.1 (t, 1H); 3.9 (s, 1H); 4.6 (, OH); 7.3 (m, 5H); ^{13}C NMR(75,47 MHz, $CDCL_3$): 14.15; 22.3; 26.22; 30.31; 37.78; 60.4; 127.40; 129.48; 136.91; 146.3; 200.65; ^{19}F NMR (282.4 MHz; $CDCl_3$): δ_F: 106.84; MS (*m/z*): 356 (M^+, 60); 231 (42); 126(31); 77(25); 61(30); 57(10). Anal Calcd for $C_{18}H_{19}F_3O_2S$: C, 60.65; H, 5.37. Found C, 60.52; H, 5.45%.

2-(4,4,4-trifluoro-1-hydroxy-2-phenyl-3-propylsulfanylbut-2-enyl) cyclohex-2-en-1-one (**6d**): Colourless oil. Yield: 50%. 28 days. IR ν (cm^{-1}): 3394 (OH); 1658 (CO); 1152 (CF_3); ^{1}H NMR (400 MHz, $CDCl_3$): 0.83 (t, 3H); 1.56 (m, 2H); 1.99 (t, 2H); 2.18 (m, 6H); 5.92 (t, 1H); 3.6 (s, 1H); 4.1 (OH); 7.1 (m, 5H); ^{13}C NMR (75,47 MHz, $CDCL_3$): 14.12; 14.25; 21.88; 26.11; 30.28; 37.41; 60.1; 127.38; 128.78; 135.98;144.8;200.65; ^{19}F NMR (282.4 MHz; $CDCl_3$): δ_F: 106.78 Anal Calcd for $C_{19}H_{21}F_3O_2S$: C, 61.59; H, 5.71. Found C, 61.59; H, 5.43%.

2-[3(dimethylamino)-4,4,4-trifluoro-1-hydroxy-2-phenylbut-2-enyl]cyclohex-en-1-one (**6e**): Colourless oil. Yield: 47%. 32 days. IR ν (cm^{-1}): 3547 (OH); 1690 (CO); 1163 (CF_3); ^{1}H NMR(400 MHz, $CDCl_3$): 2.09 (s, 6H); 2.6 (m, 6H); 4 (s, 1H); 5.8 (OH); 7.2 (t, 1H); 7.6 (m, 5H); ^{13}C NMR(75,47 MHz, $CDCL_3$): 21.32; 26.43; 29.72; 43.02; 127.95; 129.23; 129.64; 129.89; 130.24; 131.28; 135.13; 172.06; ^{19}F NMR (282.4 MHz; $CDCl_3$): δ_F: 80.93; MS (*m/z*): 339 (M^+, 10); 282 (35); 224 (68); 97 (100). Anal Calcd for $C_{18}H_{20}F_3NO_2$: C, 63.68; H, 5.94; N = 4.13. Found C, 63.64; H, 5.73; N = 4.55%.

2-[3(diethylamino)-4,4,4-trifluoro-1-hydroxy-2-phenylbut-2enyl] cyclohex-2-en-1-one (**6f**): Colourless oil. Yield: 45%. 30 days. IR ν (cm^{-1}): 3557 (OH); 1688 (CO); 1151 (CF_3); ^{1}H NMR (400 MHz, $CDCl_3$): 2 (t, 6H); 2.6 (q, 4H); 2.4 (m, 6H); 5.4 (OH); 3.9 (s, 1H); 6.1 (t, 1H); 7.4 (m, 5H); ^{13}C NMR (75,47 MHz, $CDCL_3$): 13.58**;** 22.77; 25.69; 38.25; 47.53; 60.76; 128.49; 128.5; 128.47; 128.83; 131; 138.44; 146.77; 200.38; ^{19}F NMR (282.4 MHz; $CDCl_3$): δ_F: 81; M S(*m/z*): 126 (60); 111 (29); 97 (44); 77 (78); 71 (18); 56 (40). Anal Calcd for $C_{20}H_{24}F_3NO_2$: C, 65.36; H, 6.59; N = 3.81. Found: C, 65.41; H, 6.52; N, 3.67%.

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